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13. ABSTRACT (Maximum 200 Words)

This protocol is designed to evaluate the effects of combined anti-angiogenesis and androgen ablation therapy in men at high risk for recurrence after radical prostatectomy. Both clinical (pathologic, disease-free-survival, safety) and molecular factors will be evaluated. A clinical trial to test the effectiveness of this therapy was initiated in January 2003. After a slow initial accrual, recruitment has been increasing steadily. It is still too early to evaluate the anti-cancer efficacy of combined androgen ablation and anti-angiogenesis therapy, however, the drug has been well- tolerated and there have been no surgically-related complications. As more men are enrolled and undergo treatment, we will be able to evaluate the effects of this therapy on the natural history of prostate cancer.

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ANNUAL REPORT

"Combined Neoadjuvant Anti-angiogenesis & Androgen Ablation Therapy in Men Undergoing Radical Prostatectomy" (DAMD17-02-1-0231)

August 29, 2003

INTRODUCTION

High risk localized prostate cancer (preoperative PSA>10ng/ml, >50% Gleason grade 4 (or higher) on biopsy, and bilaterally bulky palpable disease) remains inadequately treated. While surgery and radiotherapy remain the treatments of choice, many men will fail despite these curative attempts. The role of neoadjuvant systemic chemotherapy has been proposed as a means of improving disease-free survival. We have successfully used a combination of castration and squalamine, a novel anti-angiogenic agent, to eradicate tumors in a preclinical model of human prostate cancer.

In this investigator-initiated phase II clinical trial application, we proposed to extend these findings to the clinical setting. Our principal goal is to assess whether combined androgen ablation and anti-angiogenesis therapy can improve outcomes for men with poor prognostic prostate cancer undergoing radical prostatectomy. The primary objectives of this proposal are to investigate if the combination of these agents results in pathologic downstaging and downgrading of the primary tumor, if tumor recurrence can be diminished, and whether anti-angiogenic agents can be given safely in the perioperative setting. The Specific Aims are outlined in the accompanying box.

Specific Aims

1. Specific Aim 1: To test the hypothesis that combined androgen ablation and anti-angiogenesis therapy will eradicate human prostate cancer.
2. Specific Aim 2: To test the hypothesis that androgen ablation therapy renders prostate tissue more susceptible to squalamine activity by inducing changes in VEGF/VEGF-receptor and integrin expression.
3. Specific Aim 3: To test the hypothesis that neoadjuvant combined androgen ablation and anti-angiogenesis therapy will diminish post-prostatectomy disease recurrence.

BODY

To test our we hypothesize that disruption of stromal-epithelial interactions by androgen ablation renders both prostate epithelial and stromal endothelial cells more susceptible to anti-angiogenic drug activity through changes in VEGF, VEGF receptor, and integrin expression, we designed a phase II clinical trial. A schematic of the trial design is included as Figure 1.

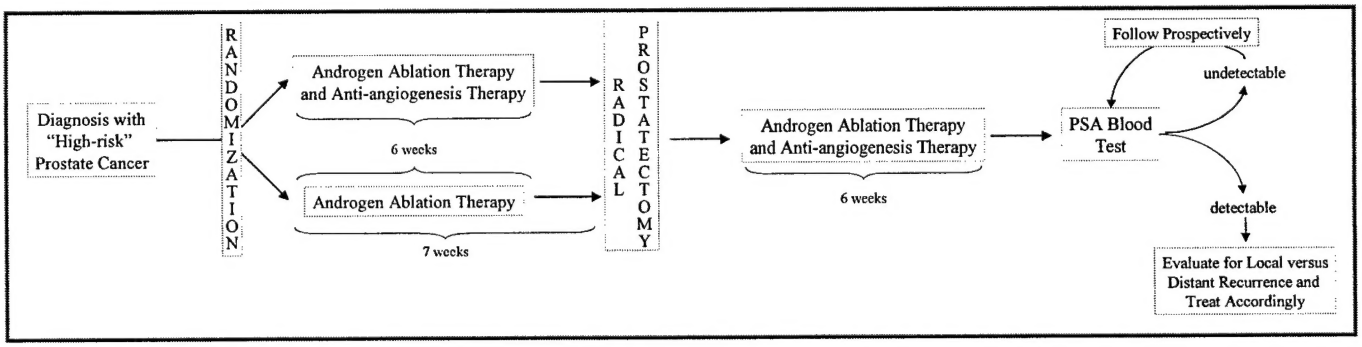


Figure 1: Schematic of clinical trial design

Preoperatively, patients will receive either androgen ablation therapy alone or combined androgen ablation and anti-angiogenesis therapy for six weeks. All patients will receive six weeks of combination androgen ablation and anti-angiogenesis therapy post-prostatectomy and will be followed prospectively for clinical evidence of disease recurrence. This randomized phase II clinical trial will investigate whether neoadjuvant combined androgen ablation and squalamine therapy is tolerable, feasible, and results in prolonged disease-free survival and pathologic downstaging and downgrading of established prostate cancers. Prostatectomy specimens will also be analyzed for changes in apoptosis, microvessel density, and VEGF, flt-1 receptor and integrin $\alpha_V\beta_3$, $\alpha_V\beta_5$ and $\alpha_6\beta_4$ expression.

This proposed clinical trial targets a population of men who are at high risk for treatment failure yet for whom there are few available therapies other than conventional surgery or radiotherapy. We will attempt to establish a role for systemic therapy for these patients, evaluate the efficacy of anti-angiogenesis therapy in prostate cancer, and validate our putative mechanisms of action which suggest that for maximum benefit, anti-angiogenesis therapy should be given in combination with androgen ablation therapy. The **Statement of Work** is summarized in the accompanying box.

STATEMENT OF WORK

Specific Aim 1: A randomized phase II clinical trial will investigate whether neoadjuvant combined androgen ablation and squalamine therapy is tolerated, feasible, and results in pathologic down-staging and downgrading of established prostate cancers.

- Task 1: Identification and enrollment of one hundred and thirty-two men with prostate cancer with characteristics denoting a "high risk" for recurrence (months 0-30)
- Task 2: Treatment of the enrolled men with either neoadjuvant androgen ablation therapy or combined neoadjuvant androgen ablation and anti-angiogenesis therapy (months 0-32)
- Task 3: Completion of radical prostatectomies on all one hundred and thirty-two men (months 2-34)
- Task 4: Evaluation of prostatectomy specimens for evidence of down-staging and down-grading (months 2-34)
- Task 5: Evaluation of safety of radical prostatectomy after treatment with an anti-angiogenic agent (months 2-36)

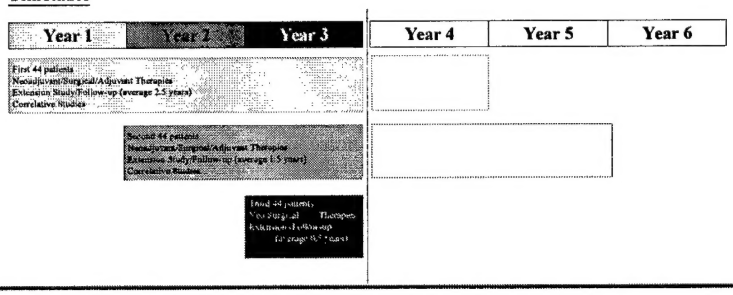
Specific Aim 2: To test the hypothesis that androgen ablation therapy renders prostate tissue more susceptible to squalamine activity by inducing changes in VEGF/VEGF-receptor and integrin expression.

- Task 6: Evaluation of prostatectomy specimens and pre-prostatectomy prostate needle biopsies for changes in apoptosis, microvessel density, and VEGF, flt-1 receptor and integrin $\alpha_V\beta_3$, $\alpha_V\beta_5$ and $\alpha_6\beta_4$ expression (months 2-36)
- Task 7: Comparison between androgen ablation alone and androgen ablation plus anti-angiogenesis treatment groups and between pretreatment (prostate needle biopsy) and post-treatment (radical prostatectomy) specimens (months 2-36)

Specific Aim 3: In an extension study, all patients will receive eight weeks of combination therapy post-prostatectomy and will be followed prospectively for clinical evidence of disease recurrence.

1. Task 8: Treatment of all enrolled men with adjuvant combined neoadjuvant androgen ablation and anti-angiogenesis therapy (months 2-36)
2. Task 9: Follow men prospectively for evidence of biochemical recurrence (months 2-36, and then through standard follow-up until month 72)

Timetable



Progress to Date

The trial official opened in January, 2003 with the first patient enrolled just six months ago (mid-February). To date, we have screened approximately 50 patients. Recruitment and accrual was slow at first. This has increased dramatically and we are now seeing at least four eligible patients weekly. To date, we have enrolled 7 men and have four others who intend to enroll once their staging studies and prostate biopsies are reviewed: we anticipate that all will qualify. Hence, including these additional patients, our accrual rate is at 50% of projected.

Of those patients screened who did not receive neoadjuvant therapy, the most common reason for not enrolling in the study included aversions to clinical trials, preference for non-surgical therapy, and ineligibility based on review of pathology.

To improve accrual, we have begun an outreach program in which community urologists and oncologists are educated on the clinical trial and encouraged to refer patients for consideration. We are also considering advertisements through the local media as part of our institutional publicity campaigns. We have seen a steady and progressive increase in interested patients and have little doubt that we will meet recruitment goals within the three years of enrollment (which will conclude in December 2005).

Only two patients treated with neoadjuvant therapy have completed their surgical treatment. Therefore, we do not yet have sufficient data to make any conclusions as to the effects of neoadjuvant combination therapy on pathologic downstaging and downgrading and changes in apoptosis, microvessel density, and VEGF, flt-1 receptor and integrin $\alpha_V\beta_3$, $\alpha_V\beta_5$ and $\alpha_6\beta_4$ expression. This data will expand and mature in the coming months and we foresee having sufficient data for presentation at the national urology and cancer research meetings next Spring. Obviously, it is too premature to evaluate disease-free progression in these two men.

Surgery has been completed safely and successfully in all men treated under the protocol and there have been no surgically-related adverse events attributable to the experimental agent. As expected, there have been standard responses to the androgen ablation therapy (hot flashes, decreased libido and sexual function, lethargy), all of which have reverse after the hormonal ablation therapy was completed. There have also been several instances of discomfort at the injection site. Nevertheless, the drug has been tolerated well and there have been no major safety concerns, to date.

KEY RESEARCH ACCOMPLISHMENTS

As the first patient was enrolled only 6 months ago and as only two patients have been thus far treated with neoadjuvant therapy, we do not yet have sufficient data to make any conclusions as to its effects on pathologic downstaging and downgrading and changes molecular factors. Likewise, it is too premature to evaluate disease-free progression. Surgery has been completed safely and successfully in all men treated under the protocol and there have been no surgically-related adverse events attributable to the experimental agent.

We have been able to refine and expand our administrative infrastructure and our recruitment methods. Although we are only at 50% of projected enrollment, this was the result of a slow start. We have seen a steady and progressive increase in interested patients and have little doubt that we will meet recruitment goals within the three years of enrollment (which will conclude in December 2005).

REPORTABLE OUTCOMES

As the first patient was enrolled only 6 months ago and as only two patients have been thus far treated with neoadjuvant therapy, we do not yet have sufficient data to make any conclusions as to its effects on pathologic downstaging and downgrading and changes molecular factors. Likewise, it is too premature to evaluate disease-free progression. We anticipate acquiring sufficient data for presentation at the national urology and cancer research meetings next Spring.

CONCLUSIONS

This proposed clinical trial targets a population of men who are at high risk for treatment failure yet for whom there are few available therapies other than conventional surgery or radiotherapy. After a delay in initiation and a slow start on accrual, our enrollment numbers are increasing and we are confident that we will meet all of our accruals. We believe that we will be able to establish a role for systemic therapy in "high risk" prostate cancer patients, conclusively evaluate the efficacy of anti-angiogenesis therapy in prostate cancer, and validate our putative mechanisms of action which suggest that for maximum benefit, anti-angiogenesis therapy should be given in combination with androgen ablation therapy.

REFERENCES

None.

APPENDICES

None.